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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,903	03/10/2004	Yuji Yamamoto	2003946-0080 (FP04-0096-0	3373

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
4173	
MAIL DATE	DELIVERY MODE
12/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/797,903	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Anna Pagonakis	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-20* is/are pending in the application.

4a) Of the above claim(s) *1-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group II and specie election of small cell lung cancer filed on 8/15/2007 is acknowledged. Additionally, the supplemental election of one compound, 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, requested telephonically by Examiner filed on 09/27/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.3(a)).

Applicant's amendment filed on 9/27/07 has been received and entered into the application. Accordingly, claims 18-20 have been added, and no claims have been cancelled or amended.

Claims 12-20 are presently under examination and are the subject of this Office Action.

Information Disclosure Statement

The information disclosure statement filed on 11/24/2004 and 12/06/2004 has been received. Documents not in English were not considered during the examination process.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which application may become aware in the specification.

Claim Objections

Applicant is advised that should claim 13 be found allowable, claim 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to other as being a substantial duplicate of an allowed claim. See MPEP 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a scope of enablement rejection. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a therapeutic method for a cancer, comprising administering to a patient suffering from a cancer "expressing excessive c-Kit kinase or a mutant c-Kit kinase." The claimed therapeutic method fails to meet the requirement for an adequate written description of the claimed invention as required by 35 U.S.C. 112, first paragraph. There is insufficient descriptive support for the generic limitation "expressing excessive c-Kit kinase or a mutant c-Kit kinase." Such a generic statement is not adequate written description of the genus because it does not distinguish the claimed genus from other except function. It also does not specifically define any of the c-Kit kinases that falls within its

definition. It does not define any of the structural features commonly possessed by members of the genus that distinguish them from others. Therefore one of skill in the art would not readily recognize the identity of the members of the c-Kit kinase genus. While Applicant has provided a general list of c-Kit kinase inhibitors, Applicant has not provided the structures or names of the c-Kit kinases themselves.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient characteristics of the c-Kit kinases. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation or any combination thereof.

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a scope of enablement rejection.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court In re Wands, 8 USPQ 2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex Parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a therapeutic method for a cancer by administering to a patient with cancer expressing c-Kit kinase or a mutant c-Kit kinase an effective dose of a c-Kit kinase inhibitor.

The breadth of the claims

The claims encompass the treatment of a cancer expressing c-Kit kinase or a mutant c-kit kinase.

The unpredictability of the art and the state of the prior art

Those of skill in the art recognize in vitro assays or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vivo or in vitro assay does not permit a single extrapolation of an in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-

dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells are derived. This has often led to tissue culture being regarded in a rather skeptical light (p4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy with characteristics profoun"ly different from the human disease. Further, Dermer teaches that when normal or malignant body cells adapt to immortal life in culture, it takes an evolutionary type step that enables the new life to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly, it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v268, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in vitro and in vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won

approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Working examples

The specification provides a single working example of administering the elected compound to the small cell lung cancer cell line H-526 expressing c-Kit kinase.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balance only against the high skill level in the art, it is the position of the examiner that would require undue experimentation of one of skill in the art to perform the method of claim as broadly written.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-20 are under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Claims 12-20 are rendered indefinite by the phrase "c-Kit." The use of the designation "c-Kit" renders the claims indefinite as the recitation is too vague. "c-Kit" is a simple acronym/abbreviation that has many different meanings in the art and thus the inclusion thereof is confusion and the claims indefinite. Applicant could simply spell out the full name in at least the first occurrence to obviate this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)

Claims 12-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funahasi et al. (WO 02/032872, cited by Applicant) in view of Hibi et al. (reference provided by Applicant).

Examiner is using the Japanese WO 02/032871 document for its publication date and is providing US Patent 7, 253, 286 as an English language equivalent of that document.

Funahasi et al. disclose the elected compound: claim 1 discloses R_1 and R_2 as hydrogen (claim 1), R^{a12} is the cyano taught by the formula in column 904, line 40, second compound, (claim 1), Y^{a1} is represented by the formula in column 903, line 35, first compound, where W^{31} and W^{32} are each independently an optionally substituted carbon atom (claim 1) and Z^{12} is an alicyclic hydrocarbon group (claim 1). This particular combination teaches the compound elected by Applicant. Additionally, Funahasi et al. describes utility of the elected compound having angiogenesis inhibitory action (column 2, lines 63-67) and tumor cell proliferation (column 83, last line) inhibitory action in treatment of diseases including as a "pulmonary treatment agent" (column 34, line 22).

Hibi et al. discloses that lung cancer cells have been known to produce autocrine growth factors which include gastrin-releasing peptide, leading the author to study c-kit expression in small cell lung cancer (page 2295, left column, paragraph 2). The researchers conclude that c-Kit expression is present in small cell lung cancer.

One of ordinary skill in the art at the time of the invention would have found it prima facie obvious to employ the results found in Hibi et al. with a reasonable expectation of success because of the clear antiproliferative activity of the elected compound (Funahasi et al.) in a variety of tumor cell lines including the elected small cell lung cancer. Motivation to do so flows logically since Hibi et al. teaches that c-Kit expression is found in small cell lung cancer and Funahasi et al. teach the elected compound as an effective treatment for pulmonary treatment.

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the inhibition of c-Kit kinase was not itself recognized

as a pharmacological effect of administering the elected compound of Funahasi et al. to a patient exhibiting proliferation of cancer cells such as small cell lung cancer, such an effect (treatment of pulmonary conditions including tumors) is already known in the prior art. Though new properties of a compound are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 103 is based upon the therapeutic applications and effects of the compounds, not the mechanisms or properties by which they exert such a therapeutic effect.

Please also see Ex Parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. And Inter. 1993), which stated, "The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of P. cepacia. A U.S. Patent to Dart disclosed inoculating using P.cepacia type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that Applicant had stated in the specification that Wisconsin 526 an 18 percent nematode inhibition rating." Analogously, in the present case, though Funahasi does not explicitly note the function of the elected compound as a c-Kit kinase inhibitor, such a property, though only now recognized by Applicant, is an inherent property of the elected compound, absent factual evidence to the contrary.

Conclusion

No claims allowed./A. P./

Examiner, Art Unit 4173

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Pagonakis whose telephone number is 571-270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin H Marschel/
Supervisory Patent Examiner, Art Unit 1614